REMARKS

With entry of this response, the claims pending are 1-2, 4-6, 8 and 12-15. Claims 3, 7, and 9-11 have been withdrawn by the Examiner as being drawn to a non-elected invention.

In the September 2, 2005 Final Office Action, the Examiner stated that the Information Disclosure Statement (IDS) filed with the application on Feb. 21, 2002 was not considered, apparently based on a failure by the PTO to record the 1449 form in the PAIR electronic filing system. Applicants herein respectfully submit that since the IDS was filed, and the exhibits therein were relied upon by Applicants in the June 27, 2005 Response to the March 30, 2005 Office Action but not considered by the Examiner, that the Final Office Action should be withdrawn.

A) The February 21, 2002 filed IDS

Applicants herein attach, refile, and resubmit the February 21, 2002 originally filed three page Information Disclosure Statement (IDS) in response to the Examiner's statement in the September 2, 2005 Office Action that said IDS did not comply with 37 CFR 1.98(a)(1) and that the information "referred to therein has not been considered". Applicants informed the Examiner by telephone on September 13, 2005 that the originally filed IDS of February 21, 2002 did indeed comply with all aspects of 37 CFR 1.98(a)(1). The Examiner explained that the PAIR system had a blank page 3 instead of the filed and filled 1449A form submitted by Applicant. The Examiner acknowledged that the originally filed page 3 of the filled out 1449A form was probably incorrectly scanned. The Examiner has thus requested re-submittal of the IDS and the references therein.

Since the information (references) in the February 21, 2002 originally filed three page Information Disclosure Statement (IDS) were not considered in the examination of

this patent application, and based upon the fact that this lack of consideration was apparently due to the PTO's failure to correctly scan the IDS into the PAIR system, Applicants respectfully request that the Final Office Action should be withdrawn. Since the cited documents therein support Applicants previously filed response of June 27, 2005 with respect to the 103(a) rejections cited by the Examiner, Applicants believe these references should be considered before an Office Action is deemed final. The argument and references relied upon by Applicant do not constitute new matter or a new search by the Examiner, as this information was timely and properly submitted to the PTO on February 21, 2002.

1. Claim rejections under 35 USC 103(a) Rejection.

The Examiner has maintained the rejection of claims 1-2, 4-6, 8 and 12-13 under § 103(a) as being unpatentable over Namiki et al (EP 0816381 A1, published on 07/01/1998) in view of Date et al (Oncogene, 17:3045-3054, 1998) and Gaertner et al (Bioconjugate 7:38-42, 1996). Applicants respectfully traverse.

The Examiner asserts that Namiki et al teach how to modify hepatocyte growth factor (HGF) by attaching a polyethylene glycol (PEG), and a pharmaceutical composition comprising the PEG modified HGF (page 12, line 37-40). However, Applicants note that Namiki only teaches the modification of HGF by attaching monoethoxy linear and branched PEG(s) at the N-terminus amino acids to improve the clearance and in vivo pharmacokinetics of HGF (page 2, line 49-57). The Examiner admits that Namiki does not teach NK4 nor the attachment of PEG with a molecular weight of 20 to 40 kDa.

The Examiner asserts that the Date reference allegedly discloses that HGF comprise, in part, a 4 kringle fragment as having NK-4. At best therefore, the combined references of Namiki and Date would not teach attachment of PEG with a molecule weight of 20 to 40 kDa at the N-terminus location.

The Examiner also asserts that Gaertner allegedly discloses attaching PEG at amino terminus of proteins and that Gaertner therefore suggests a PEG in size from 5 to 40 kDa should be attached to a protein (for an improved bioavailability), at a single attachment point using an oxime bond.

However, in contrast to the Examiner's assertions, the Nakimi reference teaches only how to modify HGF (hepatocyte growth factor) via "monoethoxy linear PEG" at the N-terminus location. As the Examiner admits, Nakimi does not teach the a) monomethoxy linear PEG addition, b) of molecular weight of 20-40kDa c) onto NK4 at the N-terminus location. The Gaertner (1996) reference merely discloses pegylation in certain proteins at N-terminal serine or threonine only sites (see e.g., Il-8 usage in Gaertner because "it has the appropriate N-terminal residue"). If the serine or threonine site is not readily available to pegylate via an oxime bond, Gaertner teaches that additional procedural steps are required to result in a serine or threonine site to pegylate. For example, Gaertner requires enzymatic cleavage/digestion of Met-Thr-Pro for the site specific pegylation of G-CSF. Gaertner also requires selective modification of the alpha amino group by metal-catalyzed transamination of Met-Arg-Pro for the site specific pegylation of IL-1ra. Gaertner acknowledges that these additional steps have drawbacks of exposing the protein to a metal, side product formation and reactions and lower yields.

In other words, Gaertner et al. merely discloses a method for the PEGylation of a terminal serine and threonine amino acid via oxime bond formation. If no serine or threonine residue is available at the N-terminus of the protein, Gaertner requires one of two procedures, 1) either additional steps are required to uncover a serine residue present within the last two amino acids of the protein (example with G-CSF) ii) or 2) additional steps involving harsh oxidation conditions have to be employed (example with IL-1ra) yielding a plurality of side products and reducing the overall yield.

The PEGylation according to Gaertner et al. is thus accomplished by the formation of an oxime bond between an N-terminally introduced carbonyl group in the protein and an aminooxy functionalized PEG. This is in contrast to the formation of an amide bond as reported in the current invention. Gaertner et al. also only teaches the attachment of linear PEG with a molecular weight of approx. 20 kDa. Gaertner does not teach, nor disclose, amide bond formation or pegylation of the N-terminal lysine group. Indeed Gaertner teaches away from lysine as a pegylation site by requiring the pegylation site to be serine or threonine, even at the cost of side product formation and reduced yield.

As Gaertner admits, the PEGylation presents a big problem if the attachment sites are not precisely controlled, as this affects protein stability and functionality. In other words, per Gaertner, it is serine or threonine, or nothing for pegylation.

Indeed, as disclosed by Applicants' specification, the Mehvar (2000) reference (which was published four years after Gaertner) states that conjugation of different polyethylene glycols to IL-8 and G-CSF as well as other interleukins results in the production of molecules with impaired properties (specification, paragraph 5). Furthermore, Francis et al. (1998) posits that "PEGylation of proteins is always based on trial and error and virtually all parameters of such a PEGylation can have a surprising and very profound effect on the functionality of the product" (specification, paragraph 6). Finally, as disclosed in our specification, Reddy (2000) states that each protein requires different optimization chemistry and therefore the influence of PEGylation cannot be predicted.

Accordingly, as the combined references do not teach nor show nor anticipate pegylation according to Applicants invention, but instead in combination actually teach away from Applicants invention. Applicants respectfully submit that claims 1-2, 4-6, 8 and 12-13 are not anticipated nor made obvious by the cited references and are thus in condition for allowance.

2. The Examiner has rejected claims 14 and 15 under 35 USC 103(a) as being unpatentable over Namiki et al (EP 0816381 A1, published on 07/01/1998) in view of Date et al (Oncogene, 17:3045-3054, 1998) and Gaertner et al (Bioconjugate 7:38-42, 1996) and further in view of the Veronese reference. The Examiner asserts that since Veronese et al disclose making PEGylated proteins and purifying them to greater than 92% purity, Veronese would teach a higher purity PEGylated protein resulting in a better bioavailability and pharmacokinetics in vivo.

However, the addition of the Veronese reference the above analysis does not render Applicants' invention obvious. Veronese merely concerns the pegylation of HGRF only. It does not address pegylation at any other protein (much less pegylation of NK4) and, in fact, only claims a peg-hgf complex that does not contain a triazine group. Indeed, and in support of Applicants' invention, Veronese specifically admits that "site-specific pegylation remains a chemical challenge."

In contrast to the current invention, Veronese et al. reports only the PEGylation of HGRF and no general method because unique coupling conditions have to be used, which are optimized for hGRF. Further, in contrast to the current invention, the PEG is coupled to the protein via a norleucine or lysine linker and not via a monomethoxy linker. Further in contrast to the current invention is a coupling of PEG to the terminal amino group only possible when all other lysine-amino-groups are protected. Still further in contrast to the current invention, Veronese et al. reports only the conjugation of a linear PEG of a molecular weight of 20 kDa. Finally, there is no motivation to combine Veronese with Gaertner, as Gaertner's specification requires the sides to be serine or threonine only. Accordingly, Applicants respectfully suggest that claims 14-15 are not anticipated nor made obvious by Veronese and are thus in condition for allowance.

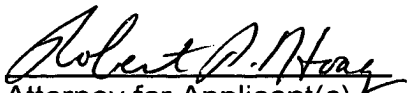
3. Conclusion

Summarizing, the current invention describes the PEGylation of an N-terminal amino acid of NK4 via amide bond formation between an N-terminal amino group and the a carboxyl group of a functionalized monomethoxy-PEG, with the molecular weight of the attached linear PEG is of between 20 kDa and 40 kDa. The cited references do not singly or in combination disclose or suggest a conjugate consisting of a NK4 molecule and a polyethylene glycol group having a molecular weight of about 20-40 kDa wherein polyethylene glycol group has: (i) the formula $-CO-(CH_2)_x-(OCH_2CH_2)_mOr$, (ii) is monomethoxy polyethylene glycol and (iii) forms amide group with the amino groups of N-terminal NK4 fragment. In contrast, the cited references teach away from Applicants invention.

For the reasons set forth above, Applicants respectfully submit that all claims 1-2, 4-6, 8 and 12-13, as herein presented, be hereby put into condition for allowance. Should the Examiner consider that outstanding issues remain unresolved, it is respectfully requested that the Examiner please telephone the undersigned attorney to discuss them.

Applicants believe that no further fee is required in connection the filing of this Amendment. If any additional fees are deemed necessary, authorization is given to charge the amount of any such fee to Deposit Account No. 08-2525.

Respectfully submitted,



Attorney for Applicant(s)
Robert P. Hoag
(Reg. No. 39712)
340 Kingsland Street
Nutley, NJ 07110
Telephone (973) 235-4453
Telefax: (973) 235-2363

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